DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 23, 2010 has been entered.

Response to Arguments

2. Applicants' arguments, filed September 23, 2010, have been fully considered but are moot in view of the new ground(s) of rejection. The following rejections and/or objections constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 4 - 6, 8 - 11, 13, 14, 21 - 29 and 33 - 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kigasawa et al. (US 4,572,832) in view of Lydzinski et al. (US 2003/0099691) and Rault et al. (US 5,900,247).

Kigasawa et al. discloses soft buccal compositions which comprise a medicament to be absorbed through the oral cavity, a water-soluble protein, a polyhydric alcohol and a fatty acid ester and/or a carboxyvinyl polymer (col 1, ln 36 –

49). Forms include sheets, bands and disks (col 6, ln 21 – 26). In example 8 (col 12, ln 43 – 60), a soft buccal comprising the active ingredient pindolol is prepared using the film forming polymer gelatin (gelatine), pH 6.5 phosphate buffer and the excipients propylene glycol, medium-chain fatty acid triglycerides, sucrose fatty acid ester glycerin, mannitol and corn starch. The total weight of the excipients is about 70% of the total weight. After sonication to create a dispersion, the gelatin was added and the resulting mixture kneaded and cut into plate-shaped (a film-shaped) dosage form. This dosage form took between 16 minutes and 17 minutes, 15 seconds to disintegrate. In example 8(a) (col 12, ln 24 – 42), gelatin was dissolved in water to which a pindolol dispersion was added, which was cut into pieces and dried to a plate like shape which was 17 mm long, 9 mm wide and 2 mm thick. This plate-shaped form took between 10 minutes, 30 seconds and 12 minutes, 40 seconds to disintegrate. Additives can be added in addition to the required ingredients, including flavorings (aroma substances) such as menthol, lemon oil and citrus flavor as well as other excipients, disintegrating adjusting agents, emulsifiers, dispersants, binders and thickeners (col 5, ln 56 – col 6, ln 6). The required polyhydric alcohol component can be ingredients such as ethylene glycol, propylene glycol, polyethylene glycol (col 4, ln 9 – 10). Also included in the category of polyhydric alcohols are cellulose and cellulose derivatives such as methyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxyethylcellulose and carboxymethyl cellulose, and polysaccahrides such as alginic acid (col 4, ln 18 – 49).

Kigasawa et al. does not disclose a matrix forming polymer as listed in claim 1 or a form with one or more aroma substances that does not include a pharmaceutical active substance.

Lydzinski et al. discloses an oral film that useful for delivering an agent to an animal or human to produce either a therapeutic or cosmetic effect, such as breath fresheners or fragrances (¶ [0006]), both of which read on the aroma substance of the instant claims. The active agent can be used in any amount desired, the only limitation being the potential load of the film, but generally, the amounts used will range from about 0.5% to about 15%, with substantially higher amounts for breath fresheners than for pharmaceutical agents (¶ [0024]). The oral film can be comprised of starch, but the starch component can also comprise cellulosic material or gums such as alginate, pullulan, carboxymethyl cellulose or carrageenan that is generally present in amount of from about 50 % to 100% exclusive of the active agent (¶ [0022]). The use of carrageenan will produce a mucoadhesive administration form.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate an aroma substance in place of the pharmaceutically active ingredient in the compositions of Kigasawa et al. and to use substances such as pullulan or carrageenan as the base mass material to produce a disintegrating oral film. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because the inclusion of an aroma substance (breath freshener or fragrance) results in an oral film that quickly disintegrates in the mouth, leaving the user with fresh or scented breath. Carrageenan

and pullulan are taught as functionally equivalent to the cellulose and alginic acid materials of Kigasawa et al. and can also be used in oral film masses. Lydzinski et al. also teaches that only an aroma substance need be present in the composition.

The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. As Lydzinski et al. teaches, almost any amount of active substance can be present in the film and the type of active ingredient will determine how much is added, with pharmaceutically active substances generally being present in lower amounts than breath freshener ingredients, so one would determine the optimal amount to add based on the particular active ingredient that is used and desired effect. The amount of matrix-forming polymer will in part determine the properties of the film, such as how it takes to dissolve. A faster dissolving film will release the active/aroma substances quickly and allow the user to eat or drink soon after taking the film without having to wait for prolonged periods of time. A shorter the disintegration time in the mouth would make it less likely that the remaining portion of the administration form would be swallowed.

Neither of the above references discloses a multi-layer administration form.

Rault et al. discloses a bioadhesive pharmaceutical composition to locally release active ingredients through various mucosal membranes (col 1, ln 7 – 15). The

bioadhesive composition comprises a vinyl acetate/polyvinylpyrrolidinone copolymer, at least one active ingredient, optionally a cellulose or cellulose derivative such as ethyl cellulose or hydroxypropylmethyl cellulose and excipients such as plasticizers, flavoring agents or sweeteners. After spreading of the bioadhesive mixture onto a biodegradable or non-biodegradable protective film or substrate, the assembly is dried (col 2, ln 54 - 62). The protective film is chosen for its adhesive or bioadhesive properties and is peelable (col 2, ln 63 – 65). This process results in the production of a multilayered administration form. In example 4, a composition is prepared which contains approximately 3% by dry weight of flavoring agents.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare a buccal administration form as taught by Kigasawa et al. and Lydzinksi et al. and to place this material on a protective film, as taught by Rault et al., resulting in a multilayered administration form. Rault et al. also provides additional guidance to one of ordinary skill in the art as to the amount of flavoring ingredients, which can include aroma substances, that can be added to such compositions.

7. Claims 1, 4 - 6, 9 - 11, 13, 14, 21 - 25, 27 - 29 and 33 -35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keith et el. (US 4,764,378) in view of in view of Lydzinski et al. (US 2003/0099691) and Rault et al. (US 5,900,247).

Keith et al. discloses buccal dosage forms for transmucosal administration of drugs (abstract) and thus the pH of the base mass of these dosage forms is approximated or adapted to the physiological values of the mucosa to which the

administration form is to be applied. The matrix comprises about 20% to about 75% of a low molecular PEG (col 3, ln 16 – 24), about 2% to about 60% of a medium to high molecular weight PEG (col 3, ln 42 – 46), about 1% to about 40% of a high molecular PEG (col 3, ln 61 – 68), about 25% to about 40% of an auxiliary polymeric ingredient such as polyvinylpyrrolidone (col 4, ln 13 – 16), minor amounts of additional ingredients such as up to about 5% of plasticizer (col 4, ln 28 – 33) and between about 0.01% and about 10% of active ingredient (col 5, ln 40 – 42). The base mass comprises PEG (polyethylene oxide) of varying molecular weights (100, 1450, 3350 and 8000); propylene glycol, a plasticizer (col 4, ln 31 - 33); and polyvinylpyrrolidone that when cut in a film, dissolves in less than 60 seconds when placed in the buccal pouch or sublingually (Example 1, col 6, ln 15 – 43). Alternatively, the high molecular weight ingredient can be sodium alginate or carboxymethyl cellulose (col 3, ln 66 - col 4, ln 12). In example 2, the base mass contains 5% of the plasticizer propylene glycol (col 6, ln 46 – 57). A variety of pharmaceutical active ingredients can be incorporated in the base material, including 5% verapamil hydrochloride (column 7, ln 1 – 6), a hydrochloride salt form of the active ingredient, resulting in a final formulation in which the polymer portion would be less than 95% (5% active ingredient, 3% propylene glycol). One formulation contained 10% by weight of the active ingredient verapamil free base (col 7, ln 38 – 42).

Keith et al. does not disclose a matrix forming polymer as listed in claim 1 or a form with one or more aroma substances that does not include a pharmaceutical active substance.

Lydzinski et al. discloses an oral film that useful for delivering an agent to an animal or human to produce either a therapeutic or cosmetic effect, such as breath fresheners or fragrances (¶ [0006]), both of which read on the aroma substance of the instant claims. The active agent can be used in any amount desired, the only limitation being the potential load of the film, but generally, the amounts used will range from about 0.5% to about 15%, with substantially higher amounts for breath fresheners than for pharmaceutical agents (¶ [0024]). The oral film can be comprised of starch, but the starch component can also comprise cellulosic material or gums such as alginate, pullulan, carboxymethyl cellulose or carrageenan that is generally present in amount of from about 50 % to 100% exclusive of the active agent (¶ [0022]). The use of carrageenan will produce a mucoadhesive administration form.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate an aroma substance in place of the pharmaceutically active ingredient in the compositions of Keith et al. and to use substances such as pullulan or carrageenan in the base mass to produce a disintegrating oral film. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because the inclusion of an aroma substance (breath freshener or fragrance) results in an oral film that quickly disintegrates in the mouth, leaving the user with fresh or scented breath. Carrageenan and pullulan are taught as functionally equivalent to the cellulose and alginate materials of Keith et al. and can also be used in oral film masses. Lydzinski et al. also teaches that only an aroma substance need be present in the composition.

The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. As Lydzinski et al. teaches, almost any amount of active substance can be present in the film and the type of active ingredient will determine how much is added, with pharmaceutically active substances generally being present in lower amounts than breath freshener ingredients, so one would determine the optimal amount to add based on the particular active ingredient that is used and desired effect. The amount of matrix-forming polymer will in part determine the properties of the film, such as how it takes to dissolve. A faster dissolving film will release the active/aroma substances quickly and allow the user to eat or drink soon after taking the film without having to wait for prolonged periods of time. A shorter the disintegration time in the mouth would make it less likely that the remaining portion of the administration form would be swallowed.

Neither of the above references discloses a multi-layer administration form.

Rault et al. discloses a bioadhesive pharmaceutical composition to locally release active ingredients through various mucosal membranes (col 1, ln 7 – 15). The bioadhesive composition comprises a vinyl acetate/polyvinylpyrrolidinone copolymer, at least one active ingredient, optionally a cellulose or cellulose derivative such as ethyl cellulose or hydroxypropylmethyl cellulose and excipients such as plasticizers, flavoring

agents or sweeteners. After spreading of the bioadhesive mixture onto a biodegradable or non-biodegradable protective film or substrate, the assembly is dried (col 2, ln 54 - 62). The protective film is chosen for its adhesive or bioadhesive properties and is peelable (col 2, ln 63 – 65). This process results in the production of a multilayered administration form. In example 4, a composition is prepared which contains approximately 3% by dry weight of flavoring agents.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare a buccal administration form as taught by Keith et al. and Lydzinksi et al. and to place this material on a protective film, as taught by Rault et al., resulting in a multilayered administration form. Rault et al. also provides additional guidance to one of ordinary skill in the art as to the amount of flavoring ingredients, which can include aroma substances, that can be added to such compositions.

8. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Keith et al. in view of Lydzinski et al. and Rault et al. as applied to claims 1, 4 - 6, 9 - 11, 13, 14, 21 - 25, 27 - 29 and 33 -35 above, and further in view of Bergeron et al. (WO 99/53897) and Gibson et al. (EP 0386960).

As discussed in greater detail above, Keith et al. discloses buccal dosage forms containing up to 10% by weight active ingredient, in a matrix-forming polymer mass. The polymer can be alginate, carboxymethyl cellulose, pullulan or carrageenan, as taught by Keith and Lydzinski. An additional protective layer can be provided to the film as taught by Rault et al.

Keith et al. does not disclose the presence of an agent that alters the pH from the Markush group of claim 8.

Bergeron et al. discloses a formulation of film-forming ingredient and an active agent for topical formulations (p 1, ln 8 – 9). The pH of the formulation can be adjusted to meet the requirements of the target tissue (p 13, ln 31 – 33). For formulations applied to the vaginal mucosa, a pH of about 4.0 – 4.5 should be used (p 13, ln 33 – 34).

Bergeron et al. does not disclose any agents that would adjust the pH depending on the target tissue.

Gibson et al. discloses that the pH of the compositions can be adjusted through the use of pharmaceutically acceptable acids or bases such as sodium or hydrochloric acid and that pH can be maintained by the use of buffering agents (p 9, ln 34 – 43).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate a pH adjusting agent in the compositions of Keith et al. The person of ordinary skill in the art would have been motivated to make those modifications, and reasonably would have expected success because Bergeron et al. discloses that the pH of the formulations should be adjusted to meet the requirements of the target tissue and Gibson et al. discloses that one way to adjust the pH is through the use of compounds such as buffer, sodium hydroxide and/or hydrochloric acid. Determining the appropriate pH and using acids, bases and/or buffers to provide a composition with that pH is within the skill of one of ordinary skill in the art.

9. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Keith in view of Lydzinski et al., Rault et al., Bergeron et al. and Gibson et al. as applied to claims 1, 4 - 6, 8 - 11, 13, 14, 21 - 25, 27 - 29 and 33 - 35 above, and further in view of Kigasawa et al. (US 4,572,832).

As discussed in greater detail above, Keith et al. discloses buccal dosage forms containing up to 10% by weight active ingredient, in a matrix-forming polymer mass. The polymer can be alginate, carboxymethyl cellulose, pullulan or carrageenan, as taught by Keith and Lydzinski. The pH can be adapted for the target tissue through the use of various ingredients. An additional protective layer can be provided to the film as taught by Rault et al.

None of the references discloses adjusting the pH using a phosphate buffer.

Kigasawa et al. discloses the adjustment of a buccal dosage form containing pindolol using phosphate buffer (example 8(b), col 12).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to adjust the pH using phosphate buffer. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because Kigasawa et al. discloses adjusting the pH of a buccal dosage form using phosphate buffer and Bergeron et al. discloses that the pH of the dosage form should be adapted to the intended administration site.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NISSA WESTERBERG whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nissa M Westerberg/
Primary Examiner, Art Unit 1618